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CRE BRIEFING PAPER ON EPA'S POLICY FOR ACCEPTABILITY OF HUMAN VOLUNTEER TEST DATA

INTRODUCTION

EPA is of the view that prior to 1998 it did not have an explicit policy or set of regulations addressing whether, or under what conditions, it would accept for regulatory purposes non-federally-funded research conducted with human volunteers, at least if such research was conducted outside the United States. It clearly did, however, have in place rules for the conduct of federally-funded research with human volunteers (EPA's version of the "Common Rule", discussed below).

On July 27, 1998, EPA issued a "Statement on Human Testing" that read, in its entirety, as follows:

> EPA is deeply concerned that some pesticide manufacturers seem to be engaging in health-effects studies on human subjects as a way to avoid more protective results from animal tests under the new Food Quality Protection Act. The government has in place very stringent standards that apply to federally funded research to ensure the protection of human subjects. EPA will be asking its independent Science Advisory Board to apply these same standards to pesticide data submitted to EPA by companies for review. No human test data has been used by EPA for any final decisions about acceptable levels of pesticide under the new food safety law. The protection of public health from adverse effects of pesticides can be achieved through reliance on animal testing and use of the highest ethical standards.

The impact of this statement was not clear from its wording, since it seems to say that non-federal human volunteer studies will be treated in the same manner as similar federally-funded studies and will be accepted if they meet the same ethical standards. In reality, it appears from recent agency statements that EPA has taken a position that its current policy is that it will not accept any non-federally-funded human volunteer test data for pesticide decisions.[1]

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[1] See articles in *The Washington Post* on June 7, 2000, page A2 ("U.S. Rejects Pesticide Tests on Humans"); in the Bureau of National Affairs *Daily Environment Report* on June 8, 2000, pages A-11 to 12 ("EPA to Maintain Ban on Use of Human Pesticide Tests for Decisionmaking"); and in the June 9, 2000 issue of *Inside EPA*, page 15 ("EPA TO REJECT HUMAN STUDIES FOR PESTICIDE TOLERANCE SETTING").

EPA did not publish this Statement in the *Federal Register* and invite comment.[2]

Shortly after the above Statement was issued, EPA convened a joint committee of its FIFRA Science Advisory Panel ("SAP") and its Science Advisory Board ("SAB") for the purpose of obtaining advice on an explicit policy for acceptance of such non-federally-funded research. Two meetings of this SAB/SAP Joint Subcommittee on Data from Human Subjects have been held, the first December 10-11, 1998, and the second on November 30, 1999. On May 23, 2000, the agency announced that the Subcommittee had prepared a report, and that the report would shortly be made available to the public and would be reviewed by the SAB Executive Committee in a public teleconference on June 16.

In preparation for the second meeting of the Joint Subcommittee held November 30, 1999, the agency issued, in addition to its "charge" to the Subcommittee (*i.e.*, specific questions to be addressed), a "Staff Background Paper" in which it amplified on its July 27, 1998 statement. The Background Paper made clear that the agency viewed the original Statement as having put in place a moratorium on acceptance of human volunteer data submitted to the pesticide program, stating –

> The Agency's policy continues as it was first articulated in July 1998: we will not rely on these studies to support final decisions under the Food Quality Protection Act [FQPA] until a policy is in place that can ensure they meet the highest scientific and ethical standards.[3]

The immediate focus in the Background Paper continued to be pesticide data, particularly that submitted in furtherance of establishing a human NOAEL (no observable adverse effects level) for acute non-cancer health effects, and it noted that the agency had received six new studies of this type since the first meeting of the Subcommittee, and a total of 14 since the passage of the FQPA in 1996. The agency also noted that it had reconsidered some of the "earlier" human studies that it had accepted in the past -- apparently prior to the FQPA -- and found them "unacceptable by contemporary scientific standards", although no further explanation was given. The Background Paper expressed, as one of the agency's "abiding concerns":

> We have never defined guidelines for testing pesticide effects or establishing NOAELs in human subjects. We do not require such studies; we do not encourage them; we do not believe them to be necessary to good risk assessments. Nevertheless the argument is

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[2] Under the Administrative Procedure Act, 5 U.S.C. § 551 *et seq*., agency statements of policy are "rules". A new rule on use of data from human volunteer trials would probably, as a legal matter, require public notice and comment under 5 U.S.C. § 553, since it would alter the FIFRA and FFDCA regulatory regimes.

[3] A very similar statement was made to the SAB/SAP Subcommittee at its November 30, 1999 meeting by the Director of the agency's pesticides program office.

made [apparently by others outside the agency] that human studies are more appropriate to an assessment of human health risk than animal studies, that they are more reliable than animal studies, and that they support more accurate assessments of potential risk.

The Background Paper also contained the following points or statements:

- The FQPA "calls for an **additional** tenfold safety factor to protect children", and use of human subject studies in place of animal studies could "**eliminate**" the tenfold inter-species uncertainty factor. This could result in pesticide residue tolerance levels higher than would otherwise be allowed, thus allowing use of more of a particular pesticide, meaning that the FQPA requirement for the additional uncertainty factor for children might have unintentionally created an incentive to test pesticides on humans. [Emphasis in quotations as in original.]

- Various offices within EPA had "continued to perform or to support many kinds of research with human subjects, with the oversight and subject protection required by the Common Rule [discussed below]."

- Since passage of the FQPA, the agency had received fourteen new studies on ten different pesticides that were "all intended to define a human systemic NOAEL".

- The agency wants "a policy that applies protections like those in the Common Rule consistently and fairly to all human research supported or considered by the Agency".

- Ethical standards have changed over time, and contemporary standards should be applied to older data. Studies performed in other countries must meet the ethical standards of our country.

- The agency's standards for ethical and scientific quality that must be met in order for a human subject study to merit consideration must be subjected to peer review and public review and comment.

The agency also submitted a "charge" to the joint subcommittee that focused primarily on ethical issues, asking how it should determine what constitutes an "ethically appropriate" human study, and whether it is ethical "to engage in oral dosing of human volunteers with environmental toxicants (*e.g.*, cryptosporidium, SOx, or organophosphates (OPs)) in order to establish a NOAEL."[4]

On June 16, 2000, the SAB/SAP Subcommittee's report will be reviewed, and possibly approved, by the SAB Executive Committee at a public teleconference. Shortly prior to then, it will be made available

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[4] Use of the term "environmental toxicants" in this context is a misnomer, since it begs the question of toxicity to humans at the exposure levels tested.

to the public. Subsequent to the end of the SAB/SAP review, the process will include, according to the agency's prior statements, at least public notice and comment on any draft rule it may propose. If finalized, the rule will also have to be submitted to Congress and the Comptroller General under the Congressional Review Act (5 U.S.C. § 801 *et seq*.), before it can take effect, and it may also have to be submitted to OMB for review as a "significant regulatory action" under Executive Order 12866.

BACKGROUND

Although other guidance is sometimes referred to, it is recognized that the primary touchstones for human volunteer testing are the Declaration of Helsinki (for the global community), and the Common Rule (for United States federal government agencies).[5]

The Declaration of Helsinki

This guidance on biomedical research involving human subjects was adopted by the World Medical Association at its Assembly in Helsinki, Finland, in 1964, and has been amended several times since then.[6] The guidance stressed that it did not relieve physicians from criminal, civil and ethical responsibilities under the laws of their own countries.

The Declaration of Helsinki is still regarded as a seminal statement. The American Medical Association is a member of the World Medical Association, and AMA publications such as *JAMA* and *Archives of Internal Medicine* give instructions to authors of research submissions who do not have formal ethics review committees that they should follow the principles outlined in the Declaration of Helsinki.

The Declaration consists of an introduction and three sets of principles: basic principles, principles for medical research on sick persons for whom there are potential diagnostic or therapeutic benefits, and principles for research where the potential benefits are not anticipated to benefit the test subjects and the aims are "purely scientific". The "basic" principles apply to both the principles on testing which is potentially therapeutic and those for testing which is "purely scientific". The key elements of the combined basic principles and principles for non-therapeutic research are:

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[5] The Declaration of Helsinki was based largely on the *Nuremberg Code*, which contained ten principles, including the need for prospects of "fruitful results for the good of society", animal experimentation as a prerequisite, informed consent, minimization of risk, and balancing of risks with humanitarian importance of the experiment.

[6] A copy of the Declaration can be obtained from many sources. One source is www.faseb.org/arvo/helsinki.htm, or see *JAMA* 277:925-26 (1997). The Association is currently considering further revisions to the Declaration, and is expected to have prepared an interim report by June 2000.

- sound scientific research methods and adequate preliminary information from laboratory and animal experimentation
- predictable hazards
- review of protocols by independent review committees
- risk in proportion to importance of objectives, with well-being of the volunteers always paramount
- informed consent and freedom to withdraw
- discontinuance of the research if it is judged that harm to the individual might result
- written confirmation of adherence to the Declaration

The "Common Rule"

Shortly after the Declaration of Helsinki was issued in 1964, the National Institutes of Health issued, in 1966, policies for the protection of human subjects. Those policies were promulgated as regulations by the Department of Health, Education, and Welfare (now the Department of Health and Human Services) in 1974. The DHEW regulations were revised in 1981 in response to the report and recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research prepared pursuant to the National Research Act of 1974 (P.L. 93-348). The National Research Act authorized the Secretary of HEW to implement the recommendations of the Commission. The HHS regulations, as further revised on June 18, 1991, were adopted, at the behest of the White House Office of Science and Technology Policy, by sixteen other federal agencies that conduct, support, or otherwise regulate human subjects research, including EPA and FDA. This commonality among federal agencies is why the HHS regulations are regularly referred to as the "the Common Rule". The HHS regulations are codified at 45 CFR Part 46; the EPA regulations are codified at 40 CFR Part 26; and the FDA regulations -- which are of particular relevance here due to their application to "Phase I" testing of human subjects -- are codified at 21 CFR Parts 50 and 56.[7]

[7] Oversight for the Common Rule within HHS is under the Office of Protection from Research Risks (OPRR), which is within the Office of the Director of the National Institutes of Health. OPRR chairs an inter-agency coordinating committee on Common Rule issues, but does not have any direct authority over other agencies. The coordinating committee is known as the Human Subjects Research Subcommittee of the Committee on Science of the National Science and Technology Council, which is administered by the White House Office of Science and Technology Policy.

The Common Rule states that it applies not only to research conducted or supported by the agency, but also research "otherwise subject to regulation by any federal department or agency. . . ." 40 CFR § 26.101(a). However, the Rule defines "Research subject to regulation" as limited to research for which an agency has specific responsibility, as in the case of FDA, and as not including "research activities which are incidentally regulated by a federal department or agency solely as part of the department or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature." 40 CFR § 26.101(e). EPA has apparently determined that pesticide research which is not conducted or supported by the agency is therefore not subject to the Common Rule. As discussed below, this fundamental point is debatable, since Congress has enacted provisions pertaining to acceptability of human subject pesticide research, and EPA periodically issues guidance for non-federal pesticide research.

The Common Rule provisions are overall very similar in principle to the contents of the Declaration of Helsinki. They simply add more detailed provisions for the composition and functioning of the independent review committees, termed "institutional review boards" ("IRBs"), documentation of compliance, and other related matters. The criteria for IRB approval of research are set out in the EPA rules at 40 CFR § 26.111. It is clear from the rules that it is not necessary that research have the potential to provide benefits to the study subjects themselves, and that the research may involve more than "minimal risk", including the potential for "injury". 40 CFR §§ 26.111(a)(2), 26.116(a)(3), 26.101(i), 26.110(b)(1), 26.116(a)(6).

It is particularly noteworthy for purposes of this briefing paper that the Common Rule explicitly addresses research conducted by non-federal institutions outside the United States. That portion of the Rule explicitly refers to the Declaration of Helsinki and provides that the agency may approve substitution of foreign procedures "in lieu of the procedural requirements provided in this policy" if the agency determines that the procedures prescribed by the foreign institution "afford protections that are at least equivalent to those provided in this policy." 40 CFR § 26.101(h).[8]

EPA's RfD risk assessment process for non-cancer health effects

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[8] The EPA's July 27, 1998 Statement was issued shortly after an environmental advocacy organization, the Environmental Working Group, published a paper titled "The English Patients" in which it questioned the ethics of conducting, outside the United States, human volunteer studies relating to pesticides. The paper stated: "Allowing human experiments, such as those conducted recently in the United Kingdom, to serve as the basis for registering pesticides, is ethically indefensible." (At p. 15.) At the same time, however, the paper appeared to endorse acceptance of human volunteer pesticide studies by EPA if the agency were able to "determine that the studies were conducted in accordance with the principles and procedures of the Common Rule." These two positions are inconsistent because the Common Rule explicitly allows for acceptance of human volunteer studies conducted abroad even if U.S. procedures were not followed, so long as the procedures followed by the foreign research institution provided equivalent protections.

Since well prior to the Common Rule, EPA has been utilizing a methodology for determining a "reference dose" (RfD) for non-cancer health effects which is based on the utilization of a number of defined "uncertainty factors" (UFs). The RfD indicates a level of exposure at which the agency expects there to be no appreciable risk of adverse health effects, although it is not intended to imply that such an exposure level is absolutely risk-free. Although the basic UFs are in increments of ten-fold reductions in exposure levels, scientific judgment may indicate a lower UF.

RfD determination depends to a great extent on whether there is adequate animal or human data, or a combination of both types of varying quality.

If there is a lack of adequate human data, the first UF is a 10x reduction in the exposure level to account for uncertainty in extrapolating from experimental animal data to humans. The essential policy assumption embedded in this UF is that humans may be more sensitive than animals, and therefore it is better to err on the side of caution.

If there is adequate human data, or if a 10x UF has been applied for extrapolation from animals to humans, another UF of 10x is applied to account for variations in susceptibility among the human population.

EPA guidance on determination of RfDs emphasizes that human data on the exposure level associated with an appropriate endpoint should be given priority over animal toxicity studies, and such human data may obviate the necessity to extrapolate from the animal data. For example, agency RfD guidance states:

> In some cases an epidemiologic study may be selected as the critical data (*e.g.*, in cases of cholinesterase inhibition). Risk assessments based on human data have the advantage of avoiding the problems inherent in interspecies extrapolation.[9]

Two additional UFs may be applied for acute effects. If the animal or human data show a LOAEL instead of a NOAEL, an additional 10x UF may be applied, based on the assumption that the actual threshold for adverse effects is somewhat lower than the observed LOAEL. Finally, a UF which is termed a "Modifying Factor" (MF) may be applied based on professional judgment regarding overall uncertainty in the data. The default value for the MF is 1, however.

Thus, in the absence of adequate human data, application of the RfD methodology to experimental animal data will result in at least a 100x reduction from an observed NOAEL, and a 1,000x reduction from a LOAEL. If there are adequate human data, the UFs might be reduced to between 10x and 100x.

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[9] "Reference Dose (RfD): Description and Use in Health Risk Assessments", EPA IRIS Background Document 1A, March 15, 1993. ("IRIS" stands for Integrated Risk Information System.)

In 1996, amendments to the Federal Food Drug and Cosmetic Act by the Food Quality Protection Act effectively modified this RfD methodology by requiring an "additional" 10x "margin of safety" to protect infants and children from pesticide residues, unless determined, on the basis of reliable data, that a different margin of safety would provide safety for infants and children.[10]

Conduct of, or support of, human volunteer tests by EPA and other federal agencies

As EPA noted in the Background Paper prepared for the 1999 SAB/SAP Subcommittee meeting, the agency has itself conducted and supported a considerable number of human volunteer experiments with potentially toxic substances. Agency and SAB/SAP sources have cited agency testing of the following substances:

- MTBE (methyl tertiary butyl ether, a gasoline additive)
- ozone
- SO_2 (sulphur dioxide)
- NO_2 (nitrogen dioxide)
- CO (carbon monoxide)
- air particulate matter and acidic particles
- methyl mercury
- hydrofluorocarbons

One of the most prominent examples of human volunteer tests for toxicity which are expressly permitted and used by the federal government are the Phase I clinical studies for investigating potential new drugs and food and color additives regulated by FDA. At the November 30, 1999 meeting of the joint SAB/SAP subcommittee, an FDA official acting as a consultant to the subcommittee made a detailed presentation on pertinent aspects of Phase I testing for INDs. Those points included the following:

- The purpose of the trial is to establish safety, not therapeutic benefits. Very few substances tested ever make it to therapeutic trials or final approval.

- Subjects do not anticipate direct personal benefits.

- Administered substances are biologically active and therefore inherently toxic at some dose.

- The studies attempt to establish a NOAEL, meaning a level at which pharmacodynamic effects are seen short of frank adverse effects and considered acceptable. The investigators will also be looking for variations from the animal data and factors such as reversibility of effects.

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[10] P.L. 104-170 (August 3, 1996), amending 21 U.S.C. §346a.

- The number of human subjects at each dose level will usually range between 3 and 10, with gradual escalation of doses until the relevant effect is observed.

- Foreign data is acceptable if considered to have been properly obtained.

Prior EPA policy and practice in accepting human volunteer studies of pesticides

Prior to its July 1998 statement on its interim policy (above), EPA had consistently accepted human volunteer pesticide safety data; there is no indication that such data were ever excluded from consideration on the basis of general policy. At the initial SAP/SAB Subcommittee meeting in December 1998, EPA representatives presented information on the agency's acceptance of such studies for the period from January 1, 1990 through August 31, 1998. During that period, 26 human effects studies based on intentional clinical exposure were submitted that addressed metabolism, pharmacokinetics, and absorption, and 8 that addressed a NOAEL. All 8 of the latter studies involved volunteer subjects, informed consent, oversight by an institutional review board, and a statement of compliance with the Declaration of Helsinki. None of the studies referred to the EPA regulations incorporating the Common Rule, and one cited the FDA regulations. The agency's materials presented to the Subcommittee did not state to what extent the agency had accepted and utilized such studies in FIFRA regulatory decisions; however, as noted previously, the agency's Background Paper presented to the SAB/SAP Subcommittee at its November 30, 1999 meeting clearly indicated that the agency had accepted human volunteer studies for use in making pesticide tolerance decisions in the past, but had recently reconsidered some of the "earlier" studies and found them unacceptable by contemporary scientific standards. Thus, at the very least it is clear that EPA has accepted some human volunteer studies for use in tolerance setting, and had never prior to July 1998 had a policy precluding or restricting use of such data.

ISSUES

Although EPA has expressed deep and abiding concerns regarding use of human volunteer data from non-federally-funded sources in making pesticide regulatory decisions, it has not specified its concerns. The agency's Background Paper submitted for the November 30, 1999 SAB/SAP Subcommittee meeting contains a section on "Agency Concerns", but it does not provide specifics regarding potential or likely deficiencies in any human volunteer studies previously submitted, nor in the Agency's use of any of those studies. The Agency's charge (list of questions to be addressed) to the SAB/SAP Subcommittee appears to focus primarily on ethics. For example, the first question posed to the panel was "What factors are relevant to consider when reaching a judgment on what constitutes an ethically appropriate human study?" The following brief discussion of issues, therefore, does not necessarily reflect EPA's or other federal agencies' views on what are the significant issues; rather, these issues have generally been compiled from a review of the SAB/SAP Subcommittee discussions.

Scientific

Although it is generally recognized that data from human studies are more relevant to assessing human safety than data from animal studies, the argument has been made that human volunteer studies should not be considered valid for purposes of establishing a NOAEL because the test subjects are generally too few (<10 for each exposure level) to have statistical validity in establishing that there will be no significant effects in the entire population exposed to residue from a pesticide.

In response, it has been argued that the numbers of animals tested are also low, and that the human data have more relevance than the animal data. Also, variability in the human population is taken into account through the 10x intra-species uncertainty factor. Finally, it is already general practice under both the Common Rule and the Declaration of Helsinki for an independent review committee to assess the scientific merits of a proposed study, and EPA scientists must exercise expert judgment regarding the weight to be given such a study. Arguing that all such studies are invalid impugns the judgment of many scientists both at EPA and in other countries who have approved or accepted such studies.

Finally, while the number of subjects in most human volunteer experiments might be considered to lack statistical significance to establish a NOAEL definitively in isolation, that does not mean that they should not be given weight in assessing the overall database as are the animal studies, nor that they should not be given weight in assessing biological effects or markers that would not be considered adverse effects. The statistical strength of human volunteer studies is no weaker than most required experimental animal studies. All relevant data should be used; human data should be considered along with, and in comparison with, animal data, not instead of available animal data. As a matter of scientific judgment, it would appear necessary to judge each case on its own merits, since different chemicals have different characteristics and mechanisms of action, have been studied previously to different degrees, and the design and objectives of each study are likely to differ considerably. In other words, scientists are capable of assessing the relevance and weight to be given certain data without the intrusion of ethical views.[11]

Policy

There is a strong implication in the controversy that there is something about pesticides that inherently distinguishes them from other chemicals in the human environment, and therefore they require different scientific or ethical standards. As some SAB/SAP Subcommittee members and consultants have pointed out, however, from a scientific perspective chemicals are chemicals and inherently capable of toxicity, whether intended to be therapeutic or pesticidal. In fact, some pesticide chemicals have therapeutic uses, and some are used directly for public health purposes to control disease-bearing insect vectors.

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[11] Some members of the SAB/SAP Subcommittee repeatedly expressed the view that a human study which is not scientifically valid is unethical. It is not necessary to reach the issue of ethics if it can be determined that the study will not yield useful scientific data. Such a study should simply be rejected at the outset on scientific grounds.

Congress has a firmly recognized in its statutes the utility, if not the necessity, of agricultural chemicals for ensuring an abundant and economical food supply as a necessary element of public health policy. As discussed below, it has also indicated express approval for the use of human volunteer test data in pesticide regulatory decisions.

Moreover, the Common Rule was promulgated pursuant to Congressional legislation, and there is no apparent logic in drawing a distinction between human volunteer studies conducted, supported, or otherwise regulated under the Common Rule and studies that meet the same standards but are not directly subject to the Common Rule either because they are privately funded or conducted in another country (recognizing, however, that the Common Rule itself covers the latter situation).

There have been suggestions that agricultural chemical companies have been motivated to use human volunteer testing as a way to "get around" the strictures of the federal food safety statutory and regulatory regime. It is very questionable whether speculation on motives should ever be a valid subject for such a debate; and a more objective assessment of the sponsors' motives would be that they want to obtain data that are of greater relevance. Moreover, it should be emphasized that the outcomes of a human experiment cannot be known beforehand (although there might be a great deal of relevant predictive data), and the human tests might show that humans are more susceptible than animals, rather than less, and a company would be legally obligated to submit such data (on greater human susceptibility) to the agency.

Since the agency's RfD approach is based on the use of relatively arbitrary "uncertainty factors", it seems only logical that it should be viewed as beneficial to reduce uncertainty through appropriate research. This is, of course, the objective of a well-designed human clinical trial. As one member of the SAB/SAP Subcommittee suggested, it could be considered unethical not to conduct human experiments under appropriate conditions as indicated in the Common Rule.

Finally, there is a broad policy issue of the legitimacy of government intrusion into fully informed and consensual private decisions. If consent is truly informed and voluntary, what is the legitimate government interest and authority for interfering in such activities, other than to determine whether the data produced is scientifically useful? As discussed below, Congress may have the authority to address this subject through legislation or authorization of regulations under its authority to provide for the general welfare (Article I, section 7 of the Constitution); however, there is no basis for federal agencies to exercise such authority without a Congressional delegation. Moreover, existing civil remedies and criminal sanctions are available to apply to verifiable instances of testing without fully informed consent, particularly if harm results. Some of these points obviously overlap considerably with certain of the legal considerations discussed below.

If EPA were to issue a formal statement of general policy regarding acceptability of human volunteer test data for FIFRA purposes, such agency action would very arguably be subject to review by OMB under Executive Order 12866 as a "significant regulatory action". Even if not directly reviewable by OMB, the Executive Order requires agency compliance with its regulatory Philosophy and Principles.

Those Principles include identification of the problem and its significance, the need for a regulatory solution, reliance on the best reasonably obtainable scientific and other information concerning the need for and consequences of the intended regulation, and consistency with other regulations.

Legal

Congress has expressly addressed the use of human volunteer research data under FIFRA. Section 12(a)(2)(P), 7 U.S.C. § 136j(a)(2)(P), which was enacted in 1972, makes it unlawful for any person –

> to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test;

This provision clearly indicates Congressional intent that human volunteer test data on pesticides would be acceptable, as a matter of ethics, if these conditions were satisfied. This provision also appears to be the basis on which EPA accepted human volunteer pesticide test data that was not supported with federal government funding for many years prior to 1998.[12]

As a result of these explicit statutory provisions, it appears that human volunteer studies involving pesticides could be considered to be "subject to regulation" by EPA within the meaning of the Common Rule as currently written.

The 1996 FQPA amendments to the Federal Food, Drug and Cosmetic Act very arguably not only permit, but require, use of relevant and reliable human volunteer test data. Section 408, as amended (21 U.S.C. § 346a(a)(2)(D)), states that EPA "shall" consider, in setting pesticide residue tolerances –

> (i) the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue in such studies; [and]
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> . . .

[12] Congressional approval of human volunteer testing is also indicated by limitations placed on research of biological agents by the Secretary of Defense, contained in 50 U.S.C. § 1520a. Those provisions prohibit testing on human subjects of chemical or biological agents, but expressly except from the prohibitions, among other things, testing for "any peaceful purpose that is related to a[n] . . . agricultural . . . activity."

> (iii) available information concerning the relationship of the results of such studies to human risk; . . . .

These provisions appear clearly to require consideration of all "available" relevant data. There is no indication that the agency would be authorized to ignore relevant human volunteer studies, particularly if they meet the conditions for such studies set out in FIFRA.

Additionally, as noted previously, the Common Rule was promulgated pursuant to Congressional authorization. On the other hand, one must ask where EPA or any other federal agency would find the legal authority to exclude from consideration relevant human data on the basis of ethical considerations other than those specified by Congress under FIFRA. Federal agencies do not have inherent regulatory powers; they operate as "agencies" of Congress, and their power to regulate must be found in some delegation of power from Congress.

Finally, as a related matter, one must question whether the agency's FIFRA Science Advisory Panel has authority to furnish advice to the agency which is based on its views of ethics rather than science. The SAP was authorized by Congress under FIFRA as an integral part of the pesticide regulatory regime (7 U.S.C. § 136w(d)). The SAP authorizing provisions in FIFRA provide only for its furnishing objective scientific advice by members who are scientists; there is no authorization to furnish policy or ethical advice, nor to include in SAP reviews individuals whose area of expertise is primarily ethics. This is reflected in the SAP's FACA charter, which provides only for furnishing of scientific advice. Under FACA, a federal advisory committee such as the SAP must operate within the scope of its charter or its actions can be given no effect. (P.L. 92-463 § 8(c), 5 U.S.C. Appendix.)

Even if it were to be assumed that EPA or another agency had the authority to reject human volunteer studies that were conducted in compliance with the statutory conditions established by Congress and those in the Common Rule, a policy to reject certain such studies that were previously considered acceptable could run afoul of the Administrative Procedure Act. It is firmly established by case law under the APA that a federal agency's departure from an established practice or policy will be considered arbitrary and capricious unless the agency announces the change along with a reasoned justification. At present, no reasoned justification for rejection of any such studies has been given by the agency. Even if the agency could provide a reasoned justification for a change in position on acceptability of human volunteer studies, any attempt to reject studies which it had accepted prior to such a change of position could be subject to even greater judicial scrutiny, particularly if such a study had played a part in a FIFRA regulatory decision and outside parties had detrimentally relied on such a decision. Presumably such studies were considered scientifically valid and relevant when accepted and used, and if that assessment is now to be changed, a clear and supportable scientific explanation for such a change must be given in order avoid a finding of arbitrary and capricious action.

CONCLUSIONS

1. Federal agencies can, and have, conducted and supported human volunteer testing of potentially toxic substances pursuant to the Common Rule under circumstances in which there was no likelihood of direct health benefits to the volunteers.

2. EPA has said that it has not used any human test data for any final decisions on acceptable levels of pesticide residues under the new food safety law. It is EPA's view that the protection of public health from adverse effects of pesticides can be achieved through reliance on animal testing and use of the highest ethical standards. EPA has not provided a reasoned basis for refusing to consider non-federal human volunteer studies of pesticides.

3. There is no rational basis for distinguishing between human volunteer studies conducted or supported by federal agencies and studies conducted or supported by non-federal entities, and the Common Rule itself already allows acceptance of such studies if conducted under the Common Rule provisions or with equivalent safeguards.

4. All federal agencies except EPA consider the Common Rule to be applicable to all types of human volunteer testing. Human testing of pesticides for non-chronic effects is very similar, for example, to FDA Phase I testing, which tests for safety rather than therapeutic benefit.

5. EPA has in the past, and continues now, to conduct human studies with potentially toxic environmental substances to determine appropriate regulatory exposure levels because it is generally recognized that data from human studies are more relevant than animal data for assessing human health.

6. Prior to its July 1998 statement of policy, EPA accepted and used human volunteer studies of pesticides that met the standards set out in the Declaration of Helsinki.

7. By ignoring existing human test data on pesticides in regulatory decision-making, EPA is in violation of FFDCA section 408, as amended (21 U.S.C. § 346a(a)(2)(D)), which requires use of all available and relevant data, and FIFRA section 12 (7 U.S.C. § 136j(a)(2)(P)), which allows use of human test data on pesticides under conditions of free and informed consent.

RECOMMENDATIONS

1. EPA should apply the Common Rule/Declaration of Helsinki to human volunteer testing conducted or supported by non-federal entities consistent with the practice and policy of all other federal health agencies.

2. EPA should abide by the FFDCA and FIFRA provisions and utilize all available and reliable data.

3. Should EPA consider a change in its past practice and policy, it must comply with the Administrative Procedure Act and obtain public input and comment on an explicit proposal, along with a clearly articulated rationale for the proposal. Until any such change is promulgated, EPA should continue its pre-1998 policy of accepting human volunteer test data that meet standards reasonably equivalent to those set out in the Common Rule.

4. When EPA issues its proposal for notice and comment, it is imperative that it announce that in the interim it will follow a policy that is consistent with the policies of other federal agencies which allow the use of human volunteer test data from non-federal entities.